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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,690	10/06/2000	David B. Weiner	UPN-3906	1044

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/680,690	WEINER ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10-13 and 34-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,10-13 and 34-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed on August 30, 2002 has been entered and assigned as Paper #11. Claims 7, 9, 14-31 have been canceled. Claims 1, 2, 4-6, 8, and 13 have been amended. Claims 32-42 are newly submitted. Claims 1-6, 8, 10-13, and 34-42 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

Claim Objections

Claims 1, 11, 12, and 42 are objected to because these claims contain subject matter drawn to a non-elected invention. The elected invention is drawn to delivering a nucleic acid, therefore, the claims should be amended so that they only read on the elected invention.

In paper #11, applicants argue that the claim 11 does not contain non-elected subject matter. However, claim recitation, "a protein complex" embraces both protein-protein complex, a protein-nucleotide complex and more, therefore, it reads on non-elected invention. It is noted the objection now applies to new claim 42.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT REQUIREMENT

Claims 1-6 and 8-13 stand rejected and claims 32-42 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In paper #11, applicants argue that the Office has not established that practice of the claimed methods would fail to result in targeted delivery of the compounds embraced by the claims, that the cited teachings of Deonariain reference does not support the proposition that targeted gene delivery is highly unpredictable, that the Capon patent is not directed to targeted gene delivery, that Hurwitz patent also fails to teach the targeted gene delivery.

In response, the arguments have been fully considered but found not persuasive for reasons of record and following.

The rejection is based on the evaluation of the knowledge of the skilled artisan in the art and the breadth of the claims, which encompass the use of a fusion comstimulatory ligand between any portion of any costimulatory ligand and any portion of any viral protein in the universe. Deonarain reference gives high hope to targeted gene delivery, but the discussed strategies are still under investigation, and at the time, they were much less efficient than viral gene delivery (Conclusion), "GENE DELIVERY BY LIGAND TARGETED RECEPTOR-MEDIATED ENDOCYTOSIS OF POLYPLEXES *SHOULD* FIND ITS WAY INTO SOME MAIN LINE GENE THERAPY TREATMENT SCHEMES... HOWEVER, IN ORDER TO ACHIEVE THE

LEVELS OF GENE TRANSFECTION AND EXPRESSION SEEN WITH RETROVIRAL VECTORS, FURTHER ADVANCES NEED TO BE MADE IN FIELDS SUCH AS MAMMALIAN ARTIFICIAL CHROMOSOMES"

(paragraph bridging pages 65-66). Deonarain did not teach fusions of viral proteins and ligands. As indicated previously, the claims broadly embrace any combination of above recited proteins in the universe, the number of such fusion ligands would be uncountable, and the function of the resulting fusion ligand thus would be unpredictable. The specification fails to provide even one such fusion ligand that would promote the delivery of a nucleic acid vector. One preferred embodiment of a fusion ligand is the extracellular region of CD28, and transmembrane and cytoplasmic regions of HIV-1 gp41 (e.g. claim 12), however, the specification is silent regarding the efficiency of the nucleic acid delivery of the ligand. The Office action (paper #9) particularly cited *Hurwitz et al* (US 5,741,492) who teach a construct that is preferably missing part or all of the transmembrane domain and /or the cytoplasmic tail domain of gp41 that leads to an enhanced vector delivery, which is somewhat contradictory to claimed invention, wherein such transmembrane and cytoplasmic regions of HIV-1 gp41 is the preferred embodiment. The example illustrated the unpredictable nature of viral proteins in the context of viral delivery. Likewise, in *Capon et al* (US 6,103,521) reference, the preferably targeting molecule is the extracellular portion of the gp41 (column 12, line 55) and intracellular portion of the CD28 (column 3, line 48), contrary to the claimed invention, these illustrations are used to support the unpredictable nature of the fusion proteins produced between a viral protein and a co-stimulating factor, not applied as prior art, thus, need not to anticipate every elements in the instant claims. The Office

does not have the facilities for testing whether each of the embodiment of applicant's invention would succeed or fail to result in the expected results. In the contrary, according to MPEP as pursuant to an enabling disclosure required by 35 U.S.C 112, first paragraph,

"AN APPLICANT'S SPECIFICATION MUST ENABLE A PERSON SKILLED IN THE ART TO MAKE AND USE THE CLAIMED INVENTION WITHOUT UNDUE EXPERIMENTATION.(...) AS SUCH, THE DISCLOSURE MUST TEACH A PERSON SKILLED IN EACH ART HOW TO MAKE AND USE THE RELEVANT ASPECT OF THE INVENTION WITHOUT *UNDUE* EXPERIMENTATION. FOR EXAMPLE, TO ENABLE A CLAIM TO A PROGRAMMED COMPUTER THAT DETERMINES AND DISPLAYS THE THREE-DIMENSIONAL STRUCTURE OF A CHEMICAL COMPOUND, THE DISCLOSURE MUST

- ENABLE A PERSON SKILLED IN THE ART OF MOLECULAR MODELING TO UNDERSTAND AND PRACTICE THE UNDERLYING MOLECULAR MODELING PROCESSES; AND

- ENABLE A PERSON SKILLED IN THE ART OF COMPUTER PROGRAMMING TO CREATE A PROGRAM THAT DIRECTS A COMPUTER TO CREATE AND DISPLAY THE IMAGE REPRESENTING THE THREE-DIMENSIONAL STRUCTURE OF THE COMPOUND.

IN OTHER WORDS, THE DISCLOSURE CORRESPONDING TO EACH ASPECT OF THE INVENTION MUST BE ENABLING TO A PERSON SKILLED IN EACH RESPECTIVE ART. (MPEP 2106.B.2)

"DETERMINING ENABLEMENT IS A QUESTION OF LAW BASED ON UNDERLYING FACTUAL FINDINGS". IN RE VAECK, 947 F.2D 488, 495, 20 USPQ2D 1438, 1444 (FED. CIR.1991); ATLAS POWDER CO. V. E.I. DU PONT DE NEMOURS & CO., 750 F.2D 1569, 1576, 224 USPQ 409, 413 (FED. CIR. 1984). One aspect of such factual evidence to be considered is "IF LITTLE IS KNOWN IN THE PRIOR ART ABOUT THE NATURE OF THE INVENTION AND THE ART IS UNPREDICTABLE, THE SPECIFICATION WOULD NEED MORE DETAIL AS TO HOW TO MAKE AND USE THE INVENTION IN ORDER TO BE ENABLING. THE "PREDICTABILITY OR LACK THEREOF" IN THE ART REFERS TO THE

ABILITY OF ONE SKILLED IN THE ART TO EXTRAPOLATE THE DISCLOSED OR KNOWN RESULTS TO THE CLAIMED INVENTION. IF ONE SKILLED IN THE ART CAN READILY ANTICIPATE THE EFFECT OF A CHANGE WITHIN THE SUBJECT MATTER TO WHICH THE CLAIMED INVENTION PERTAINS, THEN THERE IS PREDICTABILITY IN THE ART. ON THE OTHER HAND, IF ONE SKILLED IN THE ART CANNOT READILY ANTICIPATE THE EFFECT OF A CHANGE WITHIN THE SUBJECT MATTER TO WHICH THAT CLAIMED INVENTION PERTAINS, THEN THERE IS LACK OF PREDICTABILITY IN THE ART. ACCORDINGLY, WHAT IS KNOWN IN THE ART PROVIDES EVIDENCE AS TO THE QUESTION OF PREDICTABILITY. IN PARTICULAR, THE COURT IN IN RE MARZOCCHI, 439 F.2D 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), STATED: [I]N THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES WHEN THE WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE A REASONABLE DOUBT AS TO THE ACCURACY OF A PARTICULAR BROAD STATEMENT PUT FORWARD AS ENABLING SUPPORT FOR A CLAIM. THIS WILL ESPECIALLY BE THE CASE WHERE THE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES. MOST OFTEN, ADDITIONAL FACTORS, SUCH AS THE TEACHINGS IN PERTINENT REFERENCES, WILL BE AVAILABLE TO SUBSTANTIATE ANY DOUBTS THAT THE ASSERTED SCOPE OF OBJECTIVE ENABLEMENT IS IN FACT COMMENSURATE WITH THE SCOPE OF PROTECTION SOUGHT AND TO SUPPORT ANY DEMANDS BASED THEREON FOR PROOF. [FOOTNOTE OMITTED.] (MPEP 2164.02, 03)

The Office relied on the combined teachings of art of record to provide a reasonable basis to show that one skill in the art could not practice the invention without undue experimentation. Furthermore, as it is broadly claimed, the substantially uncountable numbers of costimulatory molecules have distinct chemical structures and biological functions. Thus, it would require undue experimentation for the skilled artisan to determine which of the fusion ligands could be used with respects targeted delivery of a nucleic acids.

Therefore, the rejection stands.

Claims 1-6, 8-13, and 32-42 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims now embrace introducing a nucleic acid into a cell in an individual in the presence of the CD28, and possibly other costimulatory molecues. The specification teaches co-delivery of these molecules by expressing them in a plasmid (1st paragraph, page 40, examples). In the cited references 5, and 15-17, the co-stimulatory molecules are CD80 and CD86, the ligand for CD28, the working examples are drawn to co-delivery of cytokines and chemokines. Therefore, it is noted that the teaching of the specification is silent regarding the preferred embodiment of claims, such as CD28 and gp41. It is unclear whether CD28 and its fusion proteins could promote the delivery of any nucleic acid. In view of the levels of the skilled in the art, *Guibinga et al* (J Virol 1998;72:4601-9) teach that blocking CD28 signaling pathway would enhance the cell delivery of an adenoviral vector nucleic acid (abstract), contrary to instant claims. Under the circumstance, MPEP states, "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03) When the art of record (*Guibinga et al, Capon et al and Hurwitz et al*) teaches away from the

instant claims, it is incumbent upon applicants to provide sufficient guidance within the specification to support the full scope of the invention.

The claims embrace any type of nucleic acid vectors, whereas the specification only teaches using plasmid vectors. *Deonarain* particularly teaches that receptor targeted viral vectors are inefficient for significant gene transfer. *Guibinga et al* teach blocking CD28 signaling pathway would facilitate Adv delivery. In view of such, the specification fails to provide sufficient guidance to support the full scope of the claims.

The claims also embrace delivering a non-cellular particle comprises a nucleic acid and a costimulatory ligand, wherein the ligand is a protein or polypeptide molecule, however, the specification fails to teach how to make such a particle other than co-expressing it by the nucleic acid vector, considering the unpredictable nature of the stability and the in vivo dynamics of such protein-nucleic acid complex, the specification fails to provide any teaching regarding how to make and use such complex.

With regard to the route of nucleic acid delivery, the specification is silent in this aspect. In view of the state of the art in the routes of genetic vaccination, *McCluskie et al* (Mol Med 1999 May;5:287-300) teach "ROUTES OF ADMINISTRATION OF PLASMID DNA VACCINES INFLUENCES THE STRENGTH AND NATURE OF IMMUNE RESPONSES IN MICE AND NON-HUMAN PRIMATES. HOWEVER, THE RESULTS IN MICE WERE NOT ALWAYS PREDICTIVE OF THOSE IN MONKEYS AND THIS IS LIKELY TRUE FOR HUMANS AS WELL. OPTIMAL DOSE AND IMMUNIZATION SCHEDULE WILL MOST LIKELY VARY BETWEEN SPECIES. IT IS NOT CLEAR WHETHER RESULTS IN NON-HUMAN PRIMATES WILL BE PREDICTIVE OF RESULTS IN HUMANS, THUS ADDITIONAL STUDIES ARE REQUIRED." (See abstract) *Torres et al* (J Immunol 1997;158:4529-32) teach "TRANSFECTED CELLS IN GENE GUN-BOMBARDED SKI, BUT NOT NEEDLE-INJECTED MUSCLE, PLAY A

CENTRAL ROLE IN DNA-INITIATED AB AND CTL RESPONSE" (abstract). *Nakano et al* (J Virol 1997;71:7101-09) teach that immune reactivity with plasmid DNA encoding HCV-E2 antigenic domains is linked to the injection mode, "DIFFERENT ROUTES OF INJECTION OF HCV E2 PLASMID CAN RESULT IN QUANTITATIVELY AND QUALITATIVELY DIFFERENT HUMORAL IMMUNE RESPONSES" (see abstract). In view of the state of the art with regard to general targeted vector deliver, *Deonarain* teaches that the areas of consideration when designing receptor-mediated polyplexes, including route of administration and sites of target (page 55), and further teaches, "IT IS DIFFICULT TO COMPARE THE EFFICIENCY OF DIFFERENT GENE DELIVERY SYSTEMS, ESPECIALLY BETWEEN THOSE THAT TARGET DIFFERENT RECEPTORS AS EACH DELIVERY ROUTE IS DIFFERENT" (right column page 65). In view of cited teachings, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references.

The specification fails to provide enablement for the full scope of the claims also because the targeting molecule used in the method is now drawn to CD28, whereas cells targeted are drawn to cells that express any type of costimulatory molecules, the specification fails to teach how CD28 could target a nucleic acid molecule to cells expressing any type of costimulatory molecules. the art of record teaches that CD28 is a T cell surface molecule, whereas CD80 and CD86 are ligands for CD28 (Janeways Jr.) expressed constitutive and inducibly by antigen presenting cells, in view of such, the claimed method seems only enabled to target APCs.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for selecting ligands and fusion ligands, determining the type of vectors

used, routes of delivery so that to achieve cell targeting *in vivo,* so that achieving targeted gene expression at therapeutic levels, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to ligands and fusion ligands in vector delivery and *in vivo* and *ex vivo* gene therapy of any and all diseases or disorders, and the breadth of the claims directed to the use of numerous therapeutic genes/costimulatory (fusion) ligand combinations, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-13, 32-42 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "CD28" is used by the claims to mean "a costimulatory ligand," while the accepted meaning is "T cell receptor." For example, art of record shows that CD28 is a cell surface molecule, whereas CD80 and CD86 are co-stimulatory ligand for CD28 (Janeways Jr.).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
November 15, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER